

## STATEMENT

of a thesis and an abstract on a topic "Examination of renal function in patients undergoing invasive angiographic examination with a new biomarker - neutrophilic gelatinase-associated lipocalin (NGAL)" presented of MHAT "NKB" EAD for public defense before a scientific jury for awarding a scientific and educational degree "Doctor" in a doctoral program - "Cardiology", professional field - "Medicine", field of high education - "Health and Sports" .

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Prepared the statement: Prof. Dr. Elina Trendafilova, MD, MHAT "NKB" EAD, Sofia. Elected as a member of the Scientific Jury by order № 68 / 28.02.2020 and for preparing a statement on the thesis submitted on 05.03.2020 by the members of the Scientific Jury, before which the public defense will be held. Office address: Prof. Dr. Elina Trendafilova, MD, NKB Hospital EAD

I have not found any violations in the documents attached by Dr. Iliana Petrova, the requirements of the Law on Scientific Research and Development of the Republic of Bulgaria have been met. I do not have a conflict of interest caused by my participation in the current scientific jury. I have shared scientific papers with the doctoral student among those presented for the thesis.

Data from the professional biography: Dr. Petrova graduated in medicine in 2005, since 2006 and currently works as an assistant at the National Cardiology Hospital - Sofia, has over 12 years of experience as a doctor and specialist in cardiology and invasive cardiology. Since 2016 he has been a doctoral student in independent specialization in Cardiology. Dr. Petrova is a respected and erudite cardiologist, with diverse interests and extensive clinical, organizational and teaching experience.

Assessment of the presented thesis: The problem presented for research by Dr. Petrova is extremely relevant for the modern theory and practice in cardiology and nephrology in the context of the constantly increasing contrast studies in contemporary medicine, the significant heart-kidney relationship and especially its prognostic value in terms of short and long term morbidity and mortality. Early diagnosis of contrast induced nephropathy and the possibility to predict it are essential in cardiology and nephrology.

The thesis is presented on 282 standard pages, includes 82 tables and 95 figures, and the appendices include an additional 28 tables and 13 figures. The bibliography is completely modern and contains 407 literary sources, of which 4 in Cyrillic and 403 in Latin. The abstract is presented on 87 pages and covers the requirements of the scientific organization at MHAT "NKB" EAD. The thesis was discussed and approved for public defense at a meeting of the Primary Scientific Unit at the Cardiology Clinic on 10.02.2020.

The review is up-to-date, logically structured and very detailed, presented on 89 pages, it describes the main problems in the early diagnosis of renal impairment and in particular CIN, and clearly defines the questions that await answer.

The aim of the thesis is defined as the evaluation of renal function in a group of patients undergoing routine invasive angiographic examination through plasma NGAL values in comparison

with serum creatinine and GF. The eight main tasks are well formulated and meet the set goal. The statistical methods are modern and correctly used, a large number of parameters are analyzed, which allows to make clear and concrete conclusions.

The material and methods correspond to the set goals and objectives and are correctly selected. The data of 135 patients with known or suspected coronary heart disease undergoing routine contrast angiography with clearly selected inclusion and exclusion criteria were prospectively analyzed. Patients were divided into multiple subgroups according to baseline values of NGAL, creatinine, the presence of CKD and the dynamics of the biomarker, creatinine and GF. The material is well arranged and illustrated.

The results are presented on 72 pages and are divided into 6 sections. The frequency of CIN was defined according to modern international definitions in the study population - 13.3%, and it does not differ in the two main groups - with baseline normal renal function and with CKD. The subclinical form of AKI is twice as common - 26%, established by studying the plasma values of NGAL in the general cohort of patients - in patients with baseline CKD it is 42% versus 17% in patients with baseline normal renal function in similar risk profile, angiographic data, absolute amount of contrast medium used and comorbidity, with the exception of more frequent heart failure in the groups with CIN and subclinical renal impairment. Patients with CIN and subclinical renal impairment were studied with a higher amount of contrast as a relative value to eGFR. The time to significant increase in NGAL and / or creatinine after the contrast study in the different groups was evaluated, which is important in the development of practical protocols for early diagnosis of postcontrast renal impairment. The increase in NGAL at 4 and 24 hours has a statistically significant prognostic value for early diagnosis with AUC of 0.889 and 0.870, respectively.

Additional analysis showed more frequent elevations in plasma NGAL in patients with concomitant heart failure but HF was not defined as acute or chronic, low flow or with predominant congestion, therefore the association of elevated NGAL after contrast study in patients with HF is not fully described. The association with the use of diuretics and catecholamines in the period around angiography has not been reported.

The predictive value of NGAL for the development of postcontrast renal impairment - CIN or subclinical one, was analyzed against two scales for risk assessment of CIN. Elevated NGAL values at 4 and 24 hours have a clear predictive value for the development of severe renal dysfunction.

The conclusions are 11 in number, logically and correctly formulated, followed by the data from the results and statistical analysis.

Thesis contributions: The prospective study clearly positioned NGAL as an additional and early marker of renal impairment after routine contrast testing in patients with known or suspected coronary heart disease, regardless of baseline renal function.

The author divides her contributions into two groups: theoretical-methodological and scientific-applied. I agree with this division and the contributions. For the first time in Bulgaria the diagnostic and prognostic value of NGAL is demonstrated in contrast angiographic examinations. The presence of groups with subclinical acute renal impairment, regardless of the degree of baseline renal function, was demonstrated in patients undergoing contrast angiography. Different reference

limits of plasma NGAL are established according to the stage of chronic kidney disease. The influence of concomitant diseases and risk factors on the reported levels of NGAL is demonstrated.

Critical notes: I believe that the volume of the thesis exceeds the reasonable one, as the review addresses issues such as treatment and prevention of CIN, which are not a topic of the presented research. The detailed division of multiple subgroups according to the baseline values of NGAL, creatinine and their dynamics is logical, but reduces the statistical reliability of the results. The common used drugs in included patients have effects on hemodynamics and hemodynamics parameters in relation to NGAL values has not been analyzed. These critical remarks do not diminish the merits of Dr. Petrova's thesis and its great practical significance.

Publications related to the thesis: Dr. Petrova presents 8 full-text publications in peer-reviewed journals, of which 2 in English, two chapters from published books and 7 abstracts from participation in national and international congresses.

In conclusion: The presented thesis of Dr. Iliana Petrova "Study of renal function in patients undergoing invasive angiographic examination with a new biomarker - neutrophil gelatinase-associated lipocalin (NGAL)" is an up-to-date and scientifically supported analysis of the possibilities of additional biomarker NGAL for early detection of even subclinical renal impairment in both patients with baseline CKD and patients with baseline preserved eGFR. The author goes into the details of the dynamics of this biomarker and finds that the baseline elevated values also have a prognostic value, which raises the question of its inclusion in the routine stratification of CIN risk, as well as the definition of different NGAL reference values in different stages of CKD. The association of concomitant heart failure with the increase in NGAL is implied, which is a field of further studies.

I strongly recommend the members of the Scientific Jury to positively evaluate the thesis "Study of renal function in patients undergoing invasive angiographic examination with a new biomarker - neutrophil gelatinase associated lipocalin (NGAL)" and award Dr. Iliana Hristova Petrovaya-Storova and educational degree "Doctor" in doctoral program - "Cardiology", professional field - "Medicine", field of high education - "Health and Sports".

05. 06. 2020

Prepared the statement:

Sofia

/ prof. Dr. Elina Trendafilova, MD /